subcutaneously, intravenously, orally, mucosally, submucosally or intradermally.

27. (New) The method according to claim 21 wherein the vector is a viral vector.

28. (New) The method according to claim 27 wherein the viral vector is selected from the group consisting of vaccinia based vectors, adenovirus based vectors, lenti virus based vectors and HSV based vectors.

29. (New) The method according to claim 21 wherein the vector is a plasmid.

30. (New) The method according to claim 29 wherein the plasmid is in a liposome formulation.

REMARKS/ARGUMENTS

By the present amendment, claims 1, 17 and 19 have been amended, claims 4-6, 9-12 and 16 have been cancelled, and new claims 21-30 have been added. Claims 1, 3, 7-8, 14, and 17-30 are currently pending in the application. The amendments to the claims have been made without prejudice and without acquiescing to any of the Examiner's objections. Applicants reserve the right to pursue any of the deleted subject matter in a further divisional, continuation or continuation-in-part application.

The amendment does not contain new matter and its entry is respectfully requested.

The Official Action dated July 13, 2005 has been carefully considered. It is believed that the following comments represent a complete response to the Examiner's rejections and place the present application in condition for allowance. Reconsideration is respectfully requested.

35 USC 112, first paragraph (Enablement)

The Examiner has rejected claims 1, 3-12 and 14-20 under 35 USC 112, first paragraph, for lack of enablement.

Type of Antigen

The Examiner has rejected the claims alleging that there is lack of enablement of enhancing an immune response to any antigen. In order to facilitate allowance, Applicant has amended claim 1 to a method of enhancing an immune response to a viral antigen. In addition, Applicant has added new claims 21-30, which are directed at methods of enhancing an immune response to a tumor antigen. Applicant respectfully submits that the claims as amended are enabled. For instance, Examples 8, 12, 18 and 19 provide support for viral antigens, and Examples 9-11, 13, 17 and 20-22 provide support for tumor antigens.

TAP-1 or TAP-2

The Examiner has rejected the claims for lack of enablement, alleging that a skilled artisan would not consider the transfection of either TAP-1 or TAP-2 alone into cells expressing little to no TAP-1 and TAP-2 as sufficient to enhance or increase presentation of endogenous peptide/MHC class I on the cell surface.

In response, Applicant has amended the claims and provides the following arguments. Specifically, claim 1 was amended to be directed to a method of enhancing an immune response to a viral antigen by enhancing the level of TAP-1 or TAP-2 in a cell. In addition, new claims 21-30 were added, and are directed to methods of enhancing an immune response to a tumor antigen by enhancing the level of TAP-1 in a cell.

Viral Experiments

The Examiner has stated that the Examples show that of 3 viral antigens tested, antigens derived from HSV are TAP independent, such that TAP expression did not enhance immune responses; immune response to antigens derived from Influenza virus require the expression of both TAP1 and TAP2; and only immune responses

to antigens from VSV can be enhanced by the expression of TAP1 alone.

Applicant concurs with the Examiner's finding that cells transfected with TAP-1 alone are able to present VSV antigens for an enhanced immune response as compared to non-transfected cells. Applicant respectfully submits that the VSV experiments (see Example 12) also support an enhanced immune response when the cells are transfected with TAP-2 alone. The Examiner noted that TAP-2 transfected cells showed approximately half the amount of specific lysis of the TAP-1 transfected cells. However, even though TAP-1 alone enhanced the CTL response better than TAP-2 alone, TAP-2 alone still enhanced the CTL response as compared to the untransfected cells (no TAP-1 or TAP-2 expression). Please see Example 12, Figure 14. Thus, the transfection of either TAP-1 alone or TAP-2 alone into cells was able to enhance VSV antigen presentation for an enhanced CTL response.

The Examiner has also stated that the examples show that transfection of TAP-1 alone is not sufficient to allow processing and presentation of endogenous Influenza peptides. Applicant attaches a Declaration of inventor Dr. Jefferies, which was submitted during prosecution of the patent application

United States Application no. 08/817,731. The Declaration describes experiments where CMT cells were transfected with TAP-1 (CMTr1) or TAP-2 (CMTr2). The results show that both CMTr1 and CMTr2 can present Influenza A antigens to CTLs, while the TAP deficient line CMT.64 can not. Please see Figure 3, which is attached as Exhibit E of the Declaration.

Figure 18 of the application as filed shows the results of experiments done with Influenza. Applicant respectfully points out that for each of the E:T ratios of 12.5, 25 and 50 there is an enhanced CTL response against Influenza antigens for the CMT cells expressing TAP-1 alone (CMTr1.4) as compared to the untransfected CMT cells, which are TAP-1 and TAP-2 deficient. There is greater enhancement of the CTL response seen using the CMT cells that express both TAP-1 and TAP-2 (CMTr12.12) as compared to the CMT cells expressing TAP-1 alone (CMTr1.4). However, this is likely due to the dose of Influenza used for these experiments, because the CTL response is dose dependent.

Further, the Examiner has stated that the examples show that neither TAP-1 nor TAP-2 is needed to enhance antigen presentation of cells infected with HSV. As reported in the attached article by Ahn, K. et al. (EMBO; 1996; 15(13): 3247), HSV has evolved a unique mechanism to evade the immune response.

Specifically, HSV expresses ICP47, which is a protein that inhibits TAP-mediated translocation of antigen-derived peptides across the endoplasmic reticulum. This prevents assembly of peptides with class I MHC molecules in the ER and ultimately recognition of HSV-infected cells by cytotoxic T-lymphocytes. The results of Figure 19 of the application as filed reflect this ability of HSV to evade the immune response.

In summary, Applicant has shown that either TAP-1 alone or TAP-2 alone can enhance the immune response to viral antigens. Accordingly, the Applicants respectfully submit that claim 1 and the dependent claims thereon are supported by the application.

Tumor Experiments

The Examiner has stated that the Examples do not support the transfection with TAP-2 alone to increase an anti-tumor CTL response. Specifically, the Examiner has stated that the examples show that the transfection with TAP-2 alone is not as effective to enhance a tumor specific CTL response as compared with TAP-1 alone. The Examiner has directed Applicant to Examples 21 and 22, particularly page 74.

In order to facilitate allowance, Applicant has amended claim 1 to remove reference to tumor antigens, and have added new claims

21-30. The new claims are directed to methods of enhancing an immune response to a tumor antigen by enhancing the level of TAP-1 in a cell.

In light of the above, the Applicants respectfully submit that claims 21-30 are fully enabled by the application.

Administration

The Examiner has stated that there is lack of enablement for other types of plasmid or viral vectors *in vivo*, other than recombinant vaccinia virus. In addition, the Examiner has stated there is lack of enablement for other routes of delivery of TAP into tumor cells, other than delivery to the site of the tumor. Further, the Examiner has stated that there is no guidance in the specification concerning dosages and routes of *in vivo* delivery for any and all vectors which encode TAP. Applicant respectfully traverses these objections for the following reasons.

The use of recombinant vaccinia virus is one example of how a gene encoding TAP can be introduced into a cell. A person skilled in the art will appreciate that other plasmids or viral vectors can be used. For example, please see the attached article by Dr. Jefferies (Lou, Y *et al.*, Cancer Res 2005;

65(17): 7926), which provides another example of how to express TAP in a cell. In these experiments, a nonreplicating adenovirus expressing human TAP1 was used to restore the expression of TAP1 in CMT.64 cells. Thus, Applicant respectfully submits that the application is enabled for other types of plasmid or viral vectors.

Applicant has additionally enclosed an April 26, 2001 publication in Nature by Shankaran et al. for the Examiner's review. This group administered TAP-1 intraperitoneally (i.p.) and showed that by this route of delivery mouse survival was increased. In this regard, we refer to page 519 "Contribution of TAP-1 to Cancer Therapy" and the Experimental Protocol section entitled "Generation of Effector Cell Populations" on page 520. As a result, Applicant has enabled both systemic as well as intratumoral administration of TAP molecules.

Applicant would also like to direct the Examiner to page 5, paragraph 64 and page 9, paragraphs 106-108 of the application as published. A person skilled in the art will appreciate, as described in the specification, that the dosage and routes of *in vivo* delivery can be adjusted to provide optimum therapeutic response. For example, the dosage may vary according to disease state, age, sex and weight. Further, dosage may depend on the

route of delivery. Optimal dosages and routes of delivery can be determined by trial that does not require undue experimentation.

In light of the above, the Applicants submit that the pending claims are fully supported by the application.

Genes Inducible by Tapasin

The Examiner has stated that there is lack of enablement for genes inducible by tapasin.

In order to facilitate prosecution, the Applicants have deleted claims 10 and 11 without prejudice.

In light of the above, the Applicants respectfully request that the rejection to claims 1, 3-12 and 14-20 pursuant to 35 U.S.C. 112, first paragraph for lack of enablement be withdrawn.

35 USC 112, first paragraph (Written Description)

The Examiner has rejected claim 10 pursuant to 35 U.S.C. 112, first paragraph, as lacking adequate written description for any gene which is inducible by tapasin.

As stated above, in order to facilitate prosecution the Applicants have deleted claims 10 and 11.

In light of the above, the Applicants respectfully request that the rejection to claim 10 as lacking written description pursuant to 35 U.S.C., first paragraph, be withdrawn.

35 U.S.C. 102

Spies et al. (1992)

The Examiner has rejected claims 1-5, 7-8, 16 and 19 under 35 U.S.C. 102(b) as being anticipated by Spies et al. (1992) Nature, Vol. 355, 644-646. Specifically, the Examiner has stated that Spies et al. teaches enhancement of CTL response against an LCL mutant .134, in which the TAP-1 gene is missing, but TAP-2 is present, following the co-administration of a vaccinia virus encoding a viral antigen and plasmid vector encoding TAP-1 to the cells *in vitro*. Applicant respectfully traverses this objection for the reasons given below.

Powis et al. (1991)

The Examiner has rejected claims 1-4, 6-8, 16 and 19 under 35 U.S.C. 102(b) as being anticipated by Powis et al. (1992) Nature, Vol. 354, 528-531. Specifically, the Examiner has stated that Powis et al. teaches the enhancement of CTL response

against a mutant tumor cell RMA-S, which lacks functional expression of TAP-2, following the co-administration of influenza virus, which encodes influenza viral antigens and a plasmid vector encoding TAP-2 to the cells *in vitro*. Applicant respectfully traverses this objection for the reasons given below.

Applicant respectfully submits that the present inventors have shown that TAP-1 alone or TAP-2 alone is able to enhance the processing and presentation of viral antigens. The prior art cited by the Examiner teaches that both TAP-1 and TAP-2 are required for peptide transport of viral antigens.

Applicant notes that Spies et al. used a mutant .134 cell which is missing the TAP-1 gene, but has the TAP-2 gene, and that Powis et al. used a mutant RMA-S cell, which is missing functional expression of TAP-2, but expresses TAP-1. These two references teach that both TAP-1 and TAP-2 are needed in order for viral antigen processing and presentation. In contrast, Applicant has data to show that either TAP-1 alone or TAP-2 alone can augment an immune response to viral antigens. For instance, Applicant has used CMT.64 cells which are defective in both TAP-1 and TAP-2, and have shown that augmenting the expression of either TAP-1 alone or TAP-2 alone can enhance the

presentation of viral antigens (See Examples 8-12 of the application).

In light of the above, the Applicants respectfully request that the rejection to the claims as anticipated by Spies *et al.* or Powis *et al.* be withdrawn.

Conclusion

In view of the above amendments and remarks, it is believed that this application is now in condition for allowance, and a Notice thereof is respectfully requested.

Applicants' undersigned attorney may be reached at 416-307-4161. All correspondence should continue to be directed to our address given below.

Respectfully submitted,

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